Lymphocytic Hypophysitis — Autoimmune Reaction?

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Lymphocytic hypophysitis presents clinically as a sella mass lesion with pituitary insufficiency and is radiologically indistinguishable from a pituitary tumor. Since 1962, this disease has been suspected of being an autoimmune pathologic process because of its coexistence with other autoimmune endocrine diseases. Most cases have been in females and in the puerperium or during pregnancy.

We are presenting two further cases with radiologic, endocrinologic, and surgical findings. The characterization of the tissue was performed with light microscopy, electron microscopy and immunohistochemical techniques. The T cell subsets of the lymphocytic infiltrates were studied with respect to distribution, density and in comparison to each other.

CASE REPORTS

Case 1

A 21 year old black female presented with a four month history of headaches and amenorrhea. She was five months postpartum with her first child and lactation had not resumed. There was no evidence of thyromegaly or lymphadenopathy on physical examination. Her neurologic examination was normal with the exception of minimal bitemporal hemianopia.

Her endocrinologic preoperative studies confirmed hypothyroidism, hypoadrenalism and hypogonadism. Her prolactin level, however, was in the normal range.

A CT scan demonstrated an intrasellar lesion with suprasellar extension. Angiography demonstrated no vascular abnormalities. At the time of transsphenoidal surgery, a very fibrous intrasellar lesion was resected. Her postoperative course was uneventful with the exception of the development of diabetes insipidus which was treated with DDAVP. Hormonal replacement for cortisone and thyroid was also required. Three years later this patient died in an Addisonian crisis due to lack of compliance with her medication regimen. Post mortem examination did not reveal any other endocrine gland involvement.

Case 2

A 29 year old white female presented with an eight month history of galactorrhea and amenorrhea after the delivery of her fifth child. She complained of a two
month history of a 40 pound weight loss, throbbing headaches, and decreased peripheral vision. On examination she had diffuse thymomegalgy, bilateral galactorrhea, and a bitemporal superior quadrinopias visual field defect.

The CT scan demonstrated a uniformly enhancing mass lesion in the enlarged sella. Endocrinologic studies demonstrated a cortisol of 1 mcg/dl, a free T4 of 3.6 mcg/dl, a TSH of 1 m.u./dl, and a prolactin level of 13.1 ng/ml. Adrenal cortex antibodies, antimicrosomal antibodies and antithyroglobulin antibodies were not detected.

At the time of transphenoidal surgery, an intrasellar inflammatory lesion was encountered consistent with lymphocytic adenohypophysitis. Postoperatively, she was treated with replacement DDAVP, cortisol and thyroid. Her visual field deficits improved and her galactorrhea ceased.

METHODS AND MATERIALS

Light microscopy was performed utilizing the standard hematoxylin-eosin stain. Immunoperoxidase stains for immunoreactive prolactin, growth hormone and ACTH were performed as well as electron microscopy of paraffin embedded tissue. Immunohistochemical methods employing monoclonal antibodies were used to identify B cells employing pan-B (B4) as well as kappa light chain monoclonal antibody reagents. The T cell subsets based on phenotypic markers in the lymphocytic cellular infiltrates were characterized as to pan-T cells (T3 and T4), activated T cells (T9), as well as natural killer (NK) cells, T4 (helper/inducers) cells, and T8 (suppressor/cytotoxic) cells.

RESULTS

Microscopic examination of the tissue revealed preserved acini of anterior pituitary cells separated by large numbers of inflammatory cells with both lymphocytes and plasma cells predominating. Lymphoid follicles were frequently seen with germinal center formation. The inflammatory reaction did not appear to have involved the neurohypophysis. Immunohistochemical studies demonstrated scattered cells staining positively for preserved growth hormone, prolactin and ACTH.

The histologic presence of B lymphocytes was confirmed by the B4 positive (Pan-B cell) monoclonal antibody stain as well as the demonstration of kappa light chains immunohistochemically.

The electron microscopic study of hypophyseal tissue demonstrated lymphocytes in intimate contact with pituitary epithelial cells. Some sections showed advanced damage in degenerative adenohypophysial cells.

The T cell infiltrate demonstrated a preponderance of suppressor/cytotoxic (T8) cells with less extensive staining for helper/inducer (T4) cells. This inverted relationship of helper/inducer (T4) to suppressor/cytotoxic (T8) lymphocytes in the tissue infiltrate suggested of altered immunoregulation in the pathogenesis and participation of T8 cells in the mediation of this disease.

DISCUSSION

With the inclusion of our patients, thirty-three patients have now been reported with lymphocytic hypophysitis. Fourteen cases were reported from post mortem studies and most of these were prior to the of CT scans. Thirty-two cases were in females. Only one male case has been reported (Guay et al.) and only four cases in nulliparous females. Twenty-two of twenty-eight females (79%) were
diagnosed within one year of parturition. Interestingly, twelve of twenty-four patients (43%) were primagravida.

The clinical presentations have varied from pan-hypopituitarism to single hormonal abnormalities such as hyperprolactinemia with amenorrhea and galactorrhea. However, amenorrhea/galactorrhea was not necessarily associated with elevated prolactin levels and may have resulted from hyperandrogenism or primary hypothalamic dysfunction. Symptoms of mass effect including headaches, nausea, and vomiting as well as visual field defects have been noted in over 50% of the cases. Several cases have had emotional disturbances with two of these committing suicide. Both of our patients manifested anxiety and depressive reactions.

Radiographically this lesion is indistinguishable from a pituitary adenoma. By computerized tomography scan the lesion usually enhances densely and is often associated with an enlarged sella. At the present time there are no reports in the literature of an MRI scan of this lesion.

Pathologically, the picture of lymphocytic hypophysitis appears to be related to both the chronology and extent of the pituitary lesion. The extensive cellular infiltration consists chiefly of lymphocytes with a variable number of plasma cells diffusely distributed throughout the anterior lobe of the pituitary. Immunocytochemical stains for the presence of immunoreactive growth hormone and ACTH have consistently demonstrated the preservation of surviving adenohypophysial cells. Electron microscopy of the inflammatory cell infiltrate has demonstrated interdigititation of activated lymphocytes at the common interface between pituitary cells and lymphocytes. No immune complex deposits have been identified and the blood vessels have not demonstrated pathologic changes. Although quantitative studies were not performed on our tissue preparation, there appeared to be a greater T8 lymphocytic infiltrate than T4 in the hypophyseal section. It could be that infiltrating T4 cells were present earlier and could have participated in the initiation of a local B cell response, whereas the T8 cells could be mediating the cytotoxic injury to the hypophyseal parenchymal cells.

Contrary to our observations, Jensen et al have seen an increased number of T4 cells to T8 cells in a ratio of 2:1. T4 cells were identified exclusively in the follicular regions in their case. The difference in observations could be related to the fact that our cases were studied three and five months post partum and may have had a more advanced or fulminant disease process than those studied by Jensen et al.

Recently Vanneste et al. have suggested the possibility of a preceding or concomitant lymphocytic meningitis as a possible etiologic factor in inciting hypophysitis. Documented meningoencephalitis has been associated with pituitary insufficiency and a contrast-enhancing sella suprasella mass. Jew et al. reported a case in which the resolution of the meningoencephalitis process was attended with endocrinologic and radiologic improvement. The high association of this disease with pregnancy as well as with other known autoimmune endocrine diseases suggests altered immune function. It is well known that certain presumed autoimmune pathologic processes are altered by pregnancy. This may be due to so-called fetal suppressor cell production during pregnancy that also allows the fetus to escape maternal immunologic rejection.

At the present time the management of suspected lymphoid hypophysitis should probably include a tissue biopsy and if vision is compromised, decompression of the optic chiasm. As with other autoimmune endocrine diseases, the clinical spectrum of this clinical entity might also include reversible endocrinopathies. McGrail et al. and Jensen et al. recently reported recovery of anterior pituitary function in cases of tissue biopsied hypophysitis.
With the increasing recognition and understanding of this disease process, it may become possible to recognize this entity by autoantibody detection. High dose steroids would be expected to decrease the mass effect and thereby reduce the need for surgical decompression.

References


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